

### REMARKS

Applicants thank Examiner for the Office Action of June 20, 2005. In the Office Action, pending claims 1-53 were rejected under: (1) 35 U.S.C. §112, first paragraph; (2) 35 U.S.C. §103(a) as being unpatentable over Benco (*Journal of Photochemistry and Photobiology A*, 2002) (the “Benco article”) or Kim (J. Org Chem.) (the “Kim article”) in view of U.S. Patent No. 4,659,815 to Pacey (“Pacey”) and U.S. Patent No. 6,417,005 or PCT Publication No. WO 97/39337 to Barnard (“Barnard”); and (3) the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-28 of U.S. Patent No. 6,660,526 to Benco et al. (the “’526 patent”) in view of the Benco article, Pacey and Barnard.

With this Response, Applicants have amended independent claims 1 and 16 to address Examiner’s concern that the pending claims do not require the novel compound to display lithium selectivity. Support for these amendments may be found throughout the specification as filed. The amendments comprise no new matter. In light of these amendments and following discussion, Applicants respectfully request reconsideration and allowance of pending claims 1-53.

#### Claims Rejected Under 35 U.S.C. §112, first paragraph:

The June 20, 2005 Office Action rejected claims 1-53 under 35 U.S.C. §112, first paragraph, stating:

...because the specification, while being enabling for the specifically disclosed compound, does not reasonably provide enablement for the variation in the R, X, Y and Z groups as set forth in the independent claims...First in the response filed April 4, 2005, applicant has argued that “devising a compound that will exclusively bind to one of these ions is an ***unpredictable art***”...The above statement is after applicant has characterized the claimed compound as having the components carefully selected to optimize lithium detection from sodium and potassium ions, which are characterized by applicant as being “extremely similar in structure and properties...Each if the R, X, Y and Z groups are a functionalization of either the upper or lower rims of the claimed calixarene and contain a plurality of different elements that span a wide variety of properties. Thus due to the unpredictability that applicant has argued, the single example given in the instant specification fails to

provide enablement for the large variety of structures and properties claimed in the R, X, Y, and Z groups. (June 20, 2005 Office Action; Page 2).

The current invention is a compound capable of selectively binding lithium ions over similar ions such as potassium and/or sodium ions. Due to the similarity of these structures, there is a need in the art for compounds that may selectively bind one of these ions over the competing ions.

At the time of filing the current application, the state of the art was comprised of references which disclosed azacrowns in isolation (unbound to calixarenes) having moderate lithium selectivity and azacrowns engaged to calixarenes which were optimized for potassium ion selectivity. As illustrated by the art cited in the current Office Action, no single reference discloses an azacrown engaged to a calixarene as currently claimed wherein the resulting compound could selectively bind lithium ions. Applicants put forth that at the time of filing the current application it was unknown (and certainly not obvious) to those of skill in the art how to modify an azacrown engaged to a calixarene in order to obtain a compound that could selectively bind lithium ions as compared with potassium and/or sodium ions. As illustrated by the "Background Section" of the specification, various medical conditions require the monitoring of lithium ion concentrations in a blood sample; as such, there has been a long felt need for such a device.

With the current application, the Applicants present a compound comprising an optimized azacrown which selectively binds to lithium ions over potassium and/or sodium ions. As such, the Applicants have answered the following question: How does one skilled in the art modify a compound capable of selectively binding potassium ions to a compound that does not bind potassium ions but instead binds a structurally similar ion such as lithium? The Applicants have selected substituents for R, X, Y, and Z which are structurally similar and share similar properties as compared to the specifically claimed compound (which the Office Action identifies as enabled; June 20, 2005 Office Action; Page 2). As such, these equivalents are enabled by the disclosure of the current invention.

Claims Rejected Under 35 U.S.C §103(a):

The June 20, 2005 Office Action rejected claims 1-53 under 35 U.S.C. §103(a) as being unpatentable over the Benco article or the Kim article in view of Pacey and Barnard. Applicants respectfully disagree with the Office Action's conclusion that these references disclose all elements of the claimed compound or that a motivation is present to combine the references. As such, Applicants respectfully request reconsideration and allowance of pending claims 1-53.

The Applicants have claimed a compound comprising an azacrown engaged to a calixarene. The size of the azacrown and the substituents on the calixarene were selected in order to promote lithium ion selectivity as opposed to potassium and/or sodium ion selectivity. More specifically, the azacrown comprises two oxygen molecules and the substituents are as defined by the claims.

With this Response, Applicants have amended independent claims 1 and 16 in order to require that the claimed compound "selectively binds lithium ions as compared to potassium and/or sodium ions." The current amendments were made in order to address the Examiner's concerns as stated on Page 10 of the June 20, 2005 Office Action. The remaining independent claims, claims 28 and 40, are already limited to devices and methods of utilizing lithium selective compounds. Support may be found throughout the specification as filed. More specifically, please see Page 4, Lines 4-5; Page 5, Lines 18-20.

The cited art discloses azacrowns engaged to calixarenes which have been optimized for potassium ion selectivity (the Benco article and the Kim article). These references disclose a variety of variables which may be responsible for potassium ion selectivity. Clearly, there is no motivation to modify these disclosed compounds because such a modification would render the disclosed compounds unsatisfactory for their intended purposes.

Next, the cited art includes various references which disclose azacrowns in isolation (i.e., an azacrown not engaged to a calixarene). The references show that azacrowns comprising three oxygen atoms (Pacey) have shown lithium selectivity. However, these references do not discuss how engaging an azacrown to a calixarene may alter this selectivity. Clearly, an azacrown

engaged to a calixarene should have substantially different properties as compared to an azacrown in isolation.

The cited art is discussed in detail below. The Applicants argue that no combination of these references disclose, teach or suggest an azacrown bound to a calixarene wherein the azacrown and the substituents of the calixarene have been optimized to selectively bind lithium ions as opposed to potassium and/or sodium ions. In light of the following discussion, Applicants respectfully request reconsideration and allowance of pending claims 1-53.

*The Benco Article:*

The Benco article, whose authors are three of the inventors of the present application, discloses a compound capable of selectively binding potassium ions over lithium ions and/or sodium ions. Compound II of the Benco article comprises an azacrown of four oxygen atoms engaged to a calixarene. As stated in the Office Action:

...On page 37 there is a discussion of selectivity. The first sentence of this section teaches that the eventual intention is to use molecules similar to II as a sensor. The next sentence teaches that they expect metal complexation in II to be governed by electrostatic interactions (primarily cation- $\pi$  interaction). That sentence also teaches that the selectivity is primarily controlled by a size fit effect and steric effects from the propyl substituents appended to the two rotated aryl rings of the calix[4]arene. Benco does not teach an azacrown[4]arene sized to capture lithium... (June 20, 2005 Office Action; Pages 3-4).

As stated in the Office Action, the Benco article cites various possibilities for the ability of the compound to selectively bind potassium over lithium and/or sodium ions. First, the selectivity is possible due to a size fit effect. Next, it could be due to a steric effect from the propyl substituents appended to the two rotated rings of the calix[4]arene. Further, it could be a combination of these two factors. Nowhere in the article do the authors disclose, teach or suggest that a lithium selective compound could be attained by modifying the compound in a certain way. Likewise, nowhere in the article do the authors suggest that a sodium selective compound could be attained by modifying the compound in a third way. In fact, to modify the

compound in such a way would render the compound of the Benco article “unsatisfactory for its intended purpose”—selectively binding potassium ions. As required by the M.P.E.P.:

If proposed modification would **render the prior art invention being modified** [the compound of the Benco article] **unsatisfactory for its intended purpose** [detecting potassium ions without detecting lithium ions], **then there is no suggestion or motivation to make the proposed modification**. *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984). (M.P.E.P. §2143.01)(Emphasis added).

And:

If the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, **then the teachings of the references are not sufficient to render the claims *prima facie* obvious**. *In re Ratti*, 270 F.2d 810, 123 USPQ 349 (CCPA 1959). (M.P.E.P. §2143.01)(Emphasis added).

As such, there is clearly no motivation to modify the compound of the Benco article so as to produce a compound capable of selectively binding lithium ions.

*The Kim Article:*

The Kim article discloses: (1) azacrowns in isolation (compounds 1 and 2); and (2) azacrowns engaged to calixarenes (compounds 3 and 4) which have been optimized for potassium selectivity (as in the Benco article). First, the Kim article discloses an azacrown of four oxygen molecules (compound 1) and an azacrown of five oxygen molecules (compound 2). The Kim article discloses that the azacrown of four oxygen molecules is more selective for lithium ions than the azacrown of five oxygen molecules. Second, the Kim article discloses compounds comprising an azacrown engaged to a calixarene wherein the azacrown comprises four oxygen molecules (compound 3) and an azacrown engaged to a calixarene wherein the azacrown comprises six oxygen molecules (compound 4). In comparing compound 3 to compound 4, the Kim article discloses that compound 3 showed greater potassium selectivity as compared to structure of compound 4.

In discussing the reasons responsible for potassium selectivity, the Kim article states:

From this point of view, it is possible that the combination of N-chromogenic azacrown ether and calixcrown ether would result in an optimized structure for metal ion encapsulation due to (1) electrostatic interactions between the metal ion and both the oxygens and the nitrogen as electron donors, (2)  $\pi$ -metal interactions between the metal ion and two rotated aromatic nuclei of the 1,3-alternate calixarene, and (3) an extra pendant chromogenic group attached to the nitrogen, which can promote metal complexation by 3-D encapsulation under basic conditions...(Kim article, Page 2387.)

As a conclusion, the Kim article states:

...This potassium selectivity may be due to electrostatic interaction between the metal ion and the polyether cavity composed of oxygens and nitrogens as electron donors, and  $\pi$ -metal interaction between the metal ion and two aromatic rings of the 1,3-alternate calixarene. In addition, an extra pendant chromogenic nitrophenol group attached to nitrogen may play a role in this metal complexation by encapsulation under basic conditions. (Kim article, Page 2390.)

As shown above, the Kim article discloses a list of factors which may be responsible for potassium selectivity. In light of the plurality of variables listed by the Kim article as being possibly responsible for potassium selectivity, it would not be obvious to one skilled in the art how to modify the disclosed compound from a potassium sensor to a lithium sensor of the Applicants' pending application.

In discussing the Benco article and the Kim article, the Applicants argue that the Benco article discloses a calixarene bound to an azacrown wherein the interaction between the azacrown and the calixarene provide a compound suitable for selectively detecting potassium ions over lithium ions. The Benco article lists various factors which may be responsible for the desired potassium selectivity. Next, the Kim article discloses that an azacrown (in isolation) of four oxygen atoms is moderately selective for lithium ions over potassium ions and that an azacrown (in isolation) of five oxygen atoms is moderately selective for potassium ions over lithium ions. Next, the Kim article discloses a list of variable which may be responsible for potassium selectivity when the azacrowns are engaged to calixarenes. Nowhere in either reference can one find the motivation to provide a compound which exhibits a lithium selectivity comprising a calixarene engaged to an azacrown wherein the azacrown comprises two oxygen atoms. The references attempt to optimize potassium selectivity and each recite numerous

variables which may be responsible for the resulting selectivity. As such, it would not have been obvious to one skilled in the art how to go about modifying these compounds in order to change their utility from potassium selective to lithium selective or to sodium selective, etc.

The Office Action cited the Pacey and Barnard references as curing the above-identified deficiencies. The Applicants argue that the following references do not provide the motivation to modify the compound of the Benco article and/or the Kim article from a potassium selective compound to a lithium selective compound; as such, Applicants respectfully request reconsideration and allowance of pending claims 1-53.

*Pacey:*

Pacey discloses an azacrown in isolation (not engaged to a calixarene) comprising three oxygen atoms which shows lithium selectivity. However, Pacey does not disclose: (1) an azacrown engaged to a calixarene; (2) never mentions calixarenes; or (3) what affect the substituents on a calixarene may have on lithium, potassium, and/or sodium selectivity. Pacey merely discloses that an azacrown in isolation which comprises three oxygen atoms selective to lithium ions. However, Pacey clearly does not answer questions such as: (1) will such an azacrown selectively bind to lithium when bound to a calixarene? (2) will the substituents on the calixarene play a role in the selectivity? (3) will the chromophore play a role in the selectivity? (4) will reducing the azacrown from three oxygen atoms (as is found in an unbound azacrown) to two oxygen atom (as occurs in the claimed compound) affect selectivity? In short, Pacey clearly does not answer all of the questions that are left unknown by the Benco article and the Kim article.

*Barnard:*

Barnard discloses the use of covalently immobilized fluoroionophores as optical metal ion sensors. As stated in the Office Action (page 6-page 7), Barnard discloses various types of compounds to be used in such a sensor (including structure (IV)—a calix[4]arene) as well as

various types of sensor materials (plastics, glass, etc.) However, the Barnard reference clearly does not cure the above-discussed deficiencies of the Benco article, Kim article and/or Pacey.

In light of the above-arguments, no combination of the Benco article, the Kim article, Pacey and/or Barnard disclose, teach or suggest the Applicants claimed invention. As such, Applicants respectfully request reconsideration and allowance of claims 1-53.

Claims Rejected Under Judicially Created Doctrine of Obviousness-Type Double Patenting:

The June 20, 2005 Office Action rejected claims 1-53 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-28 of U.S. Patent No. 6,660,526 (the “’526 patent”) in view of the Benco article, Pacey and Barnard, stating:

...The patented claims are directed to a molecule, device and method that encompass the molecule, device and method taught by Benco above, therefore they differ from the instant claims as the Benco reference differs from the instant claims. Thus for the reasons given above, the instant claims are obvious in view of the patented claims. (June 20, 2005 Office Action, Page 8).

The ’526 patent was based upon the Benco article; as such, the disclosure of the ’526 patent is substantially identical to the disclosure of the Benco article. Therefore, the ’526 patent discloses and claims a compound used for selectively binding potassium ions over lithium and/or sodium ions. Parallel to the argument above, modifying the compound of the ’526 patent to fall within the scope of the pending claims would render the compound of the ’526 patent “unsatisfactory for its intended purpose.” As such, the Applicants respectfully request withdrawal of the rejection of claims 1-53 under the judicially created doctrine of obviousness-type double patenting.

In this Response, Applicants have sought to distinguish the claimed compound and method from the cited art. In summary, the Benco article discloses a compound capable of selectively binding potassium ions over lithium and sodium ions. The Benco article never discloses, suggests or teaches how one skilled in the art would modify the disclosed compound in

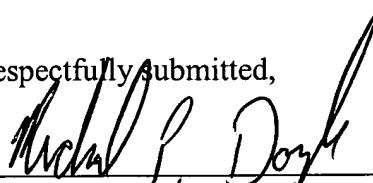
order to selectively bind lithium ions over potassium and/or sodium ions. Further, as required by the M.P.E.P., the Benco article can not provide motivation because such a modification would render the compound of the Benco article "unsatisfactory for its intended purpose." Next, the Kim article discloses that an azacrown of four oxygens is more selective towards lithium ions as opposed to an azacrown of five oxygen atoms. Next, the Kim article discloses that a calixarene bound to an azacrown of four oxygen atoms is more selective to potassium ions than a calixarene bound to an azacrown of five oxygen atoms. These references do not make the Applicants' invention obvious because the Kim references never discloses, teaches or suggests a compound comprising a calixarene engaged to an azacrown wherein the azacrown comprises two oxygen atoms (as is required by each claim of the pending application.)

Pacey merely discloses that an azacrown comprising three oxygen atoms is more selective for lithium ions as opposed to potassium ions. Pacey never discussed the effect of engaging an azacrown to a calixarene. Finally, Barnard merely discloses a sensor which comprises a calixarene. However, Barnard does not disclose, teach or suggest the compound of the claimed invention. As such, Applicants respectfully request reconsideration and allowance of pending claims 1-53.

Applicants submit that all claims are allowable as written and respectfully request early favorable action by the Examiner. If the Examiner believes that a telephone conversation with Applicants' attorney would expedite prosecution of this application, the Examiner is cordially invited to call the undersigned attorney of record.

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